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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/380,546	11/29/1999	DAVID WALLACH	WALLACH=23	2755

1444 7590 08/22/2003

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EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	34

DATE MAILED: 08/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n N .	Applicant(s)	
	09/380,546	WALLACH ET AL.	
	Examin r	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE f this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-61 and 63-71* is/are pending in the application.

4a) Of the above claim(s) *60,61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44,49-54,57,59 and 69-71* is/are rejected.

7)☒ Claim(s) *45-48,55,56,58,63-68* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *30* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Final Rejection

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/25/03 has been entered.

Claims 44-61 and 63-71 are pending.

Election/Restrictions

This application contains claims 60-61 drawn to an invention nonelected with traverse in Paper No. 13 filed on 9/17/01. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Objections

Claims 45, 46, 47, 48, 63, 64, and 68-71 are objected to because of the following informalities: the phrase "a molecule in accordance with claim" in claims 45-48, 63, 64, and 71 is in improper format for a dependent claim. Suggest replacing the phrase with -- the molecule in accordance with claim --.

The phrase "a vector in accordance with claim 49" in claims 50 and 51 is in improper format for a dependent claim. Suggest replacing the phrase with -- the vector in accordance with claim 49 --.

The phrase "a polypeptide in accordance with claim 54" in claims 55-58, 68, and 70 is in improper format for a dependent claim. Suggest replacing the phrase with -- the polypeptide in accordance with claim 54 --.

Appropriate correction is required.

Claims 65-67 are objected to because they depend on claims that are objected to for the reasons set forth above.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 44, 49-54, 59, 69, and 70 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using a DNA sequence encoding a polypeptide comprising the amino acid set forth in either SEQ ID NO: 2 or 4, or differing therefrom by one amino acid, which sequences are capable of binding to one or more of MORT-1 and MACH, and does not reasonably provide enablement for a molecule comprising a DNA sequence encoding a polypeptide which has the amino acid sequence of an analog of SEQ ID NO: 2 or 4, which differs from the sequence of SEQ ID NO: 2 or 4 more than one change in the

amino acid sequence of SEQ ID NO:2 or 4. The as-filed specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

For clarification purposes G1α is also known as CASHα and G1β is also known as CASHβ.

The specification embraces a molecule comprising a DNA sequence encoding a polypeptide and/or a polypeptide which is capable of binding to one or more of MORT-1 and MACH proteins, which polypeptide has the amino acid sequence of a fragment of a G1 protein isoform whose sequence is that of SEQ ID NO: 2 (CASHα) or 4 (CASHβ); an analog or a derivative of a G1 protein isoform whose sequence is that of SEQ ID NO: 2 or 4, which differs from the SEQ ID NO: 2 or 4 by no more than then substitutions, deletions, and/or insertions of amino acid residues and is capable of binding to one or more of MORT-1 and MACH proteins.

In view of the art of record and the as-filed specification, the specification provides sufficient guidance to make and/or use a DNA sequence comprising either SEQ ID NO: 1 or 3 and fragment thereof; or comprising the amino acid set forth in either SEQ ID NO: 2 or 4, which sequences are capable of binding to one or more of MORT-1 and MACH proteins. However, it is not apparent to one skilled in the art if any analog or derivative of a G1 protein with a nucleic acid encoding the polypeptide set forth in SEQ ID NO: 2 or 4 which differs from the protein by no more than ten changes in the amino acid sequence would possess the same biological activity

compared to the polypeptide set forth in SEQ ID NO: 2 or 4. Since, the relationship between a sequence of a peptide and its tertiary structure (i.e. its activity) is not well understood and is not predictable (e.g. see Chiu et al., *Folding and Design*, 1998, pp. 23-228), it would required undue experimentation for one skilled in the art to arrive at other peptides that have either CASHβ or CASHβ activity or bind to one or more MORT-1 or MACH proteins. Furthermore, with respect to making and using an analog which differs from the sequence of SEQ ID NO: 2 or 4 by no more than ten changes in the amino acid sequence of SEQ ID NO: 2 or 4, which analog is capable of binding to one or more of MORT-1 and MACH, the specification does not disclose the essential amino acids of SEQ ID NO: 2 or 4 that are required for binding to either MORT-1 or MACH. The art of record teaches that one amino acid substitution can cause the loss of the biologically activity of a protein. The specification does not provide sufficient guidance and/or factual evidence for what amino acids can be changed without losing the biological activity of SEQ ID NO: 2 or 4.

In addition, in *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 U.S.C. 112, first paragraph, if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for the determination of other genetic sequences that are embraced by the claim. This is the case here. In other words, since it would require undue experimentation to identify other peptides that have CASH activity, it certainty would require undue experimentation to make their corresponding DNA and, therefore

any other nucleotide sequence other than the sequence encoded by either SEQ ID NO: 1 or 3 or the DNA encoding either the polypeptide set forth in SEQ ID NO: 2 or 4 is not enabled by the specification.

In conclusion, the as-filed specification and claims coupled with the art of record at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable a DNA sequence comprising either SEQ ID NO: 1 or 3 and fragment thereof; or comprising the amino acid set forth in either SEQ ID NO: 2 or 4, which sequences are capable of binding to one or more of MORT-1 and MACH proteins and not for the full scope of the claimed invention. Given the lack of guidance for making and/or using any amino acid contemplated by the claims does not reasonably extrapolate to the full scope of the claimed invention encompassing any unknown DNA molecule encoding a mutated polypeptide of SEQ ID NOs: 2 and 4 or the amino acid sequences set forth in SEQ ID NOs: 2 and 4. Furthermore, the disclosure does not provide sufficient guidance in view of Chiu et al., *Folding and Design*, 1998, pp. 23-228 and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (Fed. Cir. 1991) for making and/or using unknown DNA sequences encoding an analog or derivative of the polypeptide set forth in SEQ ID NOs: 2 or 4.

Applicants' arguments filed on 6/10/03 have been fully considered but they are not persuasive. The traversal is not found persuasive for the following reasons: the traversal for written description is moot because the examiner did not reject any claims under written description and in view of Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991), which emphasized that the written description and enablement

requirements of 112 first paragraph, are two separate and distinct requirements that must each be met and which by direct inference, cannot form a basis for each other with regard to rejections of the claims (See MPEP 2161).

In addition, the as-filed specification fails to provide sufficient and/or factual evidence to reasonably correlate from making and/or using a DNA sequence encoding G1 protein isoform SEQ ID NOs: 2 or 4 to making and/or using an analog of any of the isoforms because of the art of record teaching the unpredictability of predicting a protein's tertiary structure from is primary sequence (Ngo et al. and Chui et al.); the applicant's journal article displaying the unpredictability of the biological activity of SEQ ID NOs: 2 and 4; and the lack of guidance for what amino acids of either SEQ ID NO: 2 or 4 are considered essential for binding to either MORT-1 and/or MACH.

In addition, in *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 U.S.C. 112, first paragraph, if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for the determination of other genetic sequences that are embraced by the claim. This is the case here. In other words, since it would require undue experimentation to identify other peptides that have CASH activity, it certainty would require undue experimentation to make their corresponding DNA and, therefore any other nucleotide sequence other than the sequence encoded by either SEQ ID NO: 2 or 4 is not enabled by the as-filed specification.

In view of the unpredictability of the two novel proteins and the lack of sufficient guidance provided by the specification for displaying the biological function of each novel protein since over-expressing a protein usually results in an unrelated function and the specification has not provided sufficient guidance to circumvent this area of concern expressed by Goltsev et al., it would require an undue amount of experimentation to determine what analogs have the ability to bind MORT-1 and/or MACH and have the same function as SEQ ID NO: 2 or 4. Furthermore, one skilled in the art understands that proteins are composed of more than one subunit and proteins that are composed of more than one subunit are found in many different classes of proteins (Phizicky et al. Microbiological Reviews, Vol. 59, pp. 94-123,1995). In view of the different subunits of a protein, a subunit from a protein that binds to SEQ ID NO: 2 or 4 in a binding assay could be from a distinct class of proteins that has a completely distinct function compared to the G1 proteins of the claimed invention. Therefore, a mere statement asserting that the assays involved to determine whether any such analog has the ability to bind MORT-1 and/or MACH are routine and all claimed analogs must possess the specified activity of being able to bind MORT and/or MACH (page 15) without providing the essential and specific arrangement of the amino acid residues positioned in the sequence does not lend evidentiary support for a skilled artisan to have recognized that applicants sufficiently described a representative number of nucleotide sequences to sufficiently represent the genus of analogs of G1 protein isoforms as claimed, particularly since the essential element of the coding sequence of a generic G1 is lacking from the as-filed specification and since the skill and knowledge in the art is not adequate or conventional to determine the primary sequence of the representative

number of species of G1 encoded genes or nucleic acids on the basis of the only disclosure of protein isoforms in either SEQ ID NOs: 2 or 4.

Thus, it is readily apparent that the as-filed specification fails to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement, e.g. Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997).

Furthermore, with respect to the assertion that doing a simple binding assay would involve no more experimentation than was approved by Wands.

The court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.
> In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

On this record, it is apparent that the specification provides no more than a plan or invitation in view of the art of record exemplifying the unpredictability of predicting the biological activity of a protein from its primary sequence and making a DNA sequence encoding a polypeptide which has the amino acid sequence of an analog of SEQ ID NO: 2 or 4, which differs from the sequence of SEQ ID NO: 2 or 4 more than one change in the amino acid sequence of SEQ ID

NO: 2 or 4, for those skilled in the art to experiment with amino acid sequences so as to provide an analog as intended by the as-filed specification at the time the invention was made.

See also Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997)

> ("Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable the public to understand and carry out the invention.")

In view of the art of record and the lack of guidance provided by the specification; the specification does not provide reasonable detail for what amino acid(s) are required for an analog of SEQ ID NO: 2 or 4 to bind to either MORT-1 or MACH protein, and it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the assertion in the specification to the full breadth of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 44, 49, 50, 51, 52, 53, 54, 57, and 69-71 remain rejected under 35 U.S.C. 102(e) as being anticipated by Shu et al. (US Patent 6,242,569, filing date 2/5/97). Shu teaches an isolated Casper protein comprising SEQ ID NO: 2 or a fragment thereof comprising SEQ ID NO: 2, residues 1-96, 1-202, 1-435, 78-480, 192-435, 192-480, 390-480 or residue, 360 joined

directly to at least 6 residues of SEQ ID NO: 2 flanking residue 360, wherein said protein specifically binds at least one of a FADD, TRAF1, TRAF2, Caspase-3, or Caspase-8 protein (column 19, claim 2). The DNA sequence encoding the amino acid sequence claimed by Shu is 99.8% identical to the applicants' claimed DNA sequence encoding SEQ ID NO: 2 and 99.8% identical to the applicants' claimed DNA sequence encoding SEQ ID NO: 4. In addition, the amino acid sequence claimed by Shu is 99.8% identical to applicants' SEQ ID NO: 2. Also, the amino acid claimed by Shu is 91% identical to applicants' amino acid SEQ ID NO: 4, but has 12 different amino acids and does not read on claim 44c or claim 54c, however, the amino acid claimed by Sul reads on claims 44b and 54b. In addition, the DNA sequence claimed by Shu is 87% identical to applicants' SEQ ID NO: 1 and 74.7% identical to SEQ ID NO: 3. Furthermore, the Caspase-8 protein is also known as the MACH protein. Shu also teaches that the proteins may be produced recombinantly from transformed host cells (abstract, column 3, lines 44-56, and column 4, lines 50-67).

Applicants' arguments filed on 10/25/02 and have been fully considered but they are not persuasive because the Declaration is ineffective to overcome the 102(e) reference.

The Declaration filed on 6/10/03 under 37 CFR 1.131 has been considered but is ineffective to overcome the 102(e) reference. There are several inventors (Andrei Kovalenko, Eugene Varfolomeev, Vadim Brodianski, David Wallach, and Yury Golstev) and only Yury Golstev has signed the Declaration. In view of the wording of the Declaration, it appears that only Yury Golstev was the inventor of the claimed invention because the wording in the Declaration indicates that he was the only inventor in possession of the polynucleotides encoding SEQ ID NO: 2 or 4. It is not apparent what the other four inventors contributed to the claims

rejected under the prior art rejection. In addition, MPEP 715 states, "the inventor of the subject matter of the rejected claim, the owner of the patent under reexamination, or the party qualified under §§ 1.42, 1.43, or 1.47, may submit an appropriate oath or declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference or activity on which the rejection is based. Andrei Kovalenko, Eugene Varfolomeev, Vadim Brodianski, David Wallach, and Yury Golstev are considered to be the inventor on this application. Thus, all of the inventors are required to sign a Declaration under 1.131.

Conclusion

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however,

will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER